Supporting documentation for the working list of NCS Core Hypotheses presented at the December, 2002 NCS Study Assembly meeting

Draft

("Rationale Document")

14 February 2003

Prepared by the NCS Interagency Coordinating Committee (ICC)

This document provides supporting information and references for the working list of NCS Core Hypotheses ratified by the ICC and presented to the NCSAC on 6 November, 2002 (see 3-page document that appears elsewhere in this volume). The 3-page working list was distributed at the December 2002 NCS Study Assembly meeting.

This introduction a) recounts the process by which these specific core hypotheses were selected, b) describes the overall context of the NCS in which the core hypotheses fit, c) discusses the implications of these hypotheses for those not listed as core, d) reviews the goals and benefits of the NCS, and e) provides an orientation to the format used in the remainder of the document. To make this a free-standing document, some of the material from the 3-page working list of core hypotheses, and other general descriptions of the NCS, appears here.

Process The overwhelming majority of these hypotheses were generated by the NCS Working Groups. Some hypotheses on the working list represent a combination of one or more hypotheses submitted by Working Groups. Other sources for hypotheses include a report prepared by the Lewin Group at the request of the ICC, and the ICC itself. Potential hypotheses were reviewed by the NCSAC in September, 2002. These reviews were considered by the ICC and played a large role in guiding the selection and development of the current set of hypotheses.

While the ICC applied the criteria for selection of core hypotheses (presented elsewhere in this briefing book--see 3-page list of core hypothesis, with selection criteria listed at the end), other considerations were influential. We sought a diverse set of hypotheses that touched on issues listed in the original Children's Health Act and that would appeal to scientists from a broad range of disciplines. We also sought to identify hypotheses that were specific and focused enough that it was reasonably clear what would need to be measured. We aimed for a collection of outcomes that would span the course of life to age 21 years. We sought compelling science and a set of hypotheses that required collection of specimens and data likely to serve multiple purposes.

Context of the NCS The NCS will be a cohort of U.S. children enrolled for study before birth, with 100,000 followed for at least 21 years. The effects of environmental factors on children will be investigated using a life-stage approach, to determine if those exposures are harmful, harmless, or helpful. A variety of environmental, medical, and social data will be collected to allow a broad investigation of the interactions of chemical, genetic, behavioral, and social factors that impact child health and development. The NCS, however, will be framed by a set of scientific hypotheses and will collect focused data to answer those questions. For all enrolled subjects, we will assess exposure to environmental agents known to adversely impact child health and development, such as exposure to lead and tobacco smoke, in order to control for those known risks while evaluating the effect of other factors. Biologic and environmental specimens will be collected to allow for assessment of exposure, subclinical health effects, and genetic studies. The data collection will be organized so as to allow evaluation of the reasons for health disparities among various groups. To validate estimates of early pregnancy exposure in the cohort, a portion of the cohort will be enrolled prior to pregnancy.

Implications for hypotheses not listed as core As can be seen in the table that immediately follows this introduction, given the data collected to address the core hypotheses on the working list, many other important hypotheses can be addressed. In our selection of core hypotheses, we excluded those for which the requisite data would be collected regardless. Thus, for example, we will be able to address the hypotheses that stress during pregnancy increases risk of preterm birth, and that air pollution increases risk of preterm birth, even though no check appears in the table. If, however, the exposure or outcome information needed to test a hypothesis is not being collected by virtue of relation to a core hypothesis, or by virtue of being a basic data item that is included in the protocol, such as lead, or tobacco smoke exposure, then after decisions are made about priorities for inclusion in the study, requisite data may not be available.

Overall Goals and Benefits of the NCS Of any study in the first half of the 21st century, the NCS will achieve the greatest progress in understanding and directing strategies to prevent a range of childhood diseases. The NCS will address many of the most pressing public health concerns in the U.S. Past studies have been unable to find cures and effective prevention strategies, but they have laid the groundwork for a study like the NCS in suggesting many risk factors and identifying genes of interest. Only a design like the longitudinal cohort can substantiate the sought after causal relationships to resolve long-standing scientific questions. The focus on multiple exposures and multiple outcomes represents both a powerful scientific tool as well as a budgetary efficiency. The depth of analysis across both common and less common exposures and genotypes simultaneously means that the complete picture of what causes and prevents disease will come into focus.

Orientation to format used in the remainder of this document The discussion of each hypothesis (or group of hypotheses) begins with a statement of the magnitude of the problem, outlining the burden each outcome and exposure has on the U.S. population. Current knowledge addressing the hypothesis is briefly summarized in the state of the science section, followed by a sketch of ways in which the NCS can collect data to advance that knowledge. The sample size calculations provide a rough guide to assist in the evaluation of the ability of a study of the size proposed for the NCS to address each hypothesis (or group of hypotheses). The calculations are simple and do not consider interactive effects or stratified analyses. In addition, each calculation assumes a population of 100,000, regardless of the stage of the study at which the outcome is assessed.

Our working list of core hypotheses can be improved, and we especially look forward to additional input on hypotheses regarding injury, and health services related to asthma. We also recognize that as hypotheses are translated into a specific protocol, balancing science and feasibility with respect to subject burden will challenge us.

Intersection of exposures and outcomes among core hypotheses on the working list, with outcomes arranged approximately by chronological period of life course[*]

	Birth Defects	Preterm Birth	Cerebral Palsy/Autism	Neuro-cognitive	Injury	Asthma	Obesity	Puberty	Schizo-phrenia
Impaired glucose metabolism	✔						✔		
Inflammation/ infection		✔	✔						✔
Nonpersistent pesticides				✔					
Air pollution						✔			
Bioaerosols						✔			
Respiratory viral infection						✔			
Maternal stress						✔			
Diet						✔	✔		
Health Services						✔			
Intrauterine growth restriction							✔		
Breastfeeding/ breastmilk							✔		
Built environment							✔		
Social and behavioral							✔		
Other pollutants								✔	

[*] Checks appear only when a specific core hypothesis involves a given exposure and outcome. See introduction for further discussion.

1. Hypothesis Among women without diabetes before pregnancy, impaired glucose metabolism during pregnancy is proportional to risk of major congenital malformations of the heart, central nervous system, musculoskeletal system, and all birth defects combined.

Magnitude of the Problem The prevalence at birth of major congenital malformations of the heart is about 0.6% (Hoffman and Kaplan, 2002), of central nervous system defects is about 0.3% (NCS ICC, 2003), and of musculoskeletal birth defects is about 0.2% (NCS ICC, 2003). The prevalence of all major birth defects combined is about 3-4% (Leppig et al. 1987; Lynberg and Edmonds, 1994). The estimated lifetime cost of birth defects, among children born during one year in the United States, is, for heart defects, central nervous defects, and musculoskeletal defects combined, $2 billion; and for all birth defects combined is $8 billion (1992 dollars; MMWR, 1995).

State of the Science Among women who have type 1 or type 2 diabetes before pregnancy the risk of congenital anomalies in offspring is increased, and animal models confirm the teratogenicity of impaired glucose metabolism. Whether women first diagnosed with diabetes during pregnancy (gestational diabetes) or those with lesser degrees of impaired glucose metabolism during pregnancy have offspring with increased frequency of birth defects has not been determined, though limited data suggest an association (Farrell, 2002; Schafer, 1997). Estimates of the prevalence of gestational diabetes vary, but figures of 4 to 7 percent have recently been reported (Naylor et al. 1996). Furthermore, as the prevalence of overweight increases among women of child-bearing age (Mokdad, et al, 1999), a parallel increase in the prevalence of gestational diabetes is expected (Kjos and Buchanan, 1999). Thus, new information about gestational diabetes and birth defects is timely. The three specific birth defects listed above are among the most common defects seen in offspring of diabetic women. While an association between impaired glucose metabolism and birth defects in general is expected, we have focused on specific defects since the relationship is likely to vary among anomalies arising from different cell lines and stages of embryonic development.

How the NCS will address the problem Prenatal assessment of gestational diabetes and maternal glucose metabolism will be done as early as possible during pregnancy, according to a standardized protocol for all women. Biologic specimens for assessment of serum glucose, Hgb A1c, and serum insulin levels may be utilized. Linkage to clinical records may also facilitate ascertainment of diabetes and serum glucose levels. All infants born into the study will undergo a standardized examination including assessments of birth defects. The results could affect recommendations regarding prepregnancy screening for impaired glucose metabolism and regarding management of glucose metabolism during early pregnancy.

Sample size considerations: This basic power calculation is a simple example based on the prevalence of diagnosed gestational diabetes, and does not consider a continuous relationship between maternal serum glucose levels and risk of birth defects. Note that 80% power, with a two-sided alpha level of 0.05, will be used for all power calculations in this document. Assuming 100,000 infants are born into the study, with a prevalence of

gestation diabetes of 5%, the smallest detectable relative risks will be, for heart defects, 1.6; for central nervous system defects, 1.8; and for musculoskeletal defects, 2.1

2. Hypothesis: Intrauterine exposure to mediators of inflammation due to infection of either vaginal, cervical, or uterine sites, or of more distal sites (e.g., periodontal disease) is associated with an increased risk of preterm birth.

Magnitude of the problem: Each year in the United States, almost 500,000 infants, approximately 12% of all births, are born preterm (<37 weeks gestation) (Martin, et al. 2002). Two-thirds of all infant deaths in the US occur among those born preterm and preterm birth is associated with substantial neonatal morbidity, a high risk of long-term neuro-developmental deficits, and low academic achievement (Hack, et al. 2002). A report based on 1988 data estimated an annual incremental increase of $6 billion in health care, education, and child care costs attributable to children <15 years born low-birthweight, compared to if they had been normal-birthweight (Lewitt, et al. 1995). (69% of low-birthweight children are born preterm [Savitz et al. 2000]). This underestimates current costs because of increasing preterm birth rates and improved survival of preterm infants. Due to large socioeconomic and racial or ethnic disparities, the US population does not evenly share the medical, education, and economic costs of preterm birth. For instance, black infants have twice the risk of preterm birth than do non-Hispanic white infants.

State of the science: The cause of most preterm births is unclear. However, over the past 20 years the potential contribution of infection to spontaneous preterm birth has gained increasing attention. Evidence of placental or chorioamniotic infection is present in up to 40% of all spontaneous preterm births and in up to 75% of those before 32 weeks gestation, the infants at greatest risk of subsequent adverse outcome (Romero, et al. 2002; Andrews, et al. 2000)., compared to approximately 1-2% among infants born term (Wu and Colford 2000). Numerous common organisms of generally low virulence (e.g., ureaplasma, mycoplasma, gardenerella) have been associated with spontaneous preterm birth. Perhaps more intriguing is the association of chorioamoniotic or vaginal markers of inflammation and infection (e.g., IL-1, IL-6, TNF-α, fetal fibronectin) with preterm birth in the absence of identifiable infectious agents. In addition, recent reports of potential associations between periodontal disease and preterm birth raise additional questions about the mechanism of local and systemic infection and inflammation on spontaneous preterm birth (Offenbacher, et al.). There has been a "consistent failure of interventions to prevent preterm birth in the United States" (Andrews, et al. 2000), including interventions aimed at treating or preventing maternal-fetal infections.

How the NCS will address the problem: Collection of biologic samples during pregnancy will enable assessment of the influence of timing and chronicity of infection on preterm birth. Samples may include cervical and vaginal cultures and histologic material obtained starting as early in pregnancy as possible. Those samples, as well as serum and urine, can also be assessed for a variety of cytokines and other local and systemic inflammatory markers. At birth, placental material and cord blood can be examined for indications of infection and inflammation. Linkage to obstetric records may provide other evidence of infection.

Results of the NCS may lead to targeted interventions aimed at decreasing preterm birth, and subsequent morbidity and mortality, by both the prevention and treatment of maternal-fetal infection and related inflammation. Such interventions may help reduce the large disparities in risk among various population groups present in the US. A related benefit will be the reduction of adverse neurobehavioural outcomes thought to be related to intra-uterine infection, such as cerebral palsy or perhaps autism, not always mediated through preterm birth.

Sample size considerations: This example does not consider stratified analyses designed to examine sub-population differences in the relationship between infection or inflammation and preterm birth, nor does it consider examination of potential gene-exposure interactions.

Assuming a sample size of 100,000 pregnancies, incidence of very preterm birth (<32 weeks) of 2%, prevalence of intrauterine infection of 2%, the smallest detectable relative risk will be approximately 1.5.

3. Hypothesis Repeated, low-level exposure to nonpersistent pesticides *in utero* or postnatally increases risk of poor performance on neurobehavioral and cognitive examinations during infancy and later in childhood, especially, for certain agents, among those with genetically decreased paraoxonase activity.

Magnitude of the Problem National survey data show that the general adult population has widespread exposure to pesticides, as reflected by levels of urinary metabolites (Hill et al., 1995). In many settings, children have greater opportunity for exposure due to their greater dermal contact with surfaces near the floor or ground, and because of their greater hand-to-mouth activity. Indeed, in the few studies that are available about children's exposures to pesticides, as reflected by the levels of urinary metabolites, exposure was surprisingly frequent, even in populations without agricultural exposure.

Because children may be more sensitive than adults to low levels of neurotoxic substances, and because exposure is widespread, vigilance about the potential health effects is prudent. This prudence is merited despite the recent regulation to decrease use of organophosphate pesticides in homes, because other pesticides with similar mechanisms are still used in homes. Organophosphate pesticides are also used extensively in agriculture and children's exposure from food sources is substantial (Curl, et al. 2003)

State of the Science Experiments on animals that show that low levels of organophosphate pesticides *in utero* or postnatally have subtle, detrimental, and permanent effects on behavior (Eskenazi, 1999). Their toxicity owes to inhibition of cholinesterase (Brimijoin, 1999), an action shared also by carbamate pesticides. The lowest level of organophosphate exposure used in these experiments (Muto, 1992) resulted in exposures that were within an order of magnitude of what humans experience in buildings where pesticides are used (Currie, 1990).

About half of an English population studied had the genotype for a less active isoform of paraoxonase, an enzyme that hydrolyzes organophosphates (Cherry et al., 2002). Another study showed a similar distribution of genotype in an Asian population (Padungtod et al. 1999). While some evidence suggests that people with different isoforms vary with respect to risk of neurotoxicity from organophosphates (Cherry et al., 2002), the possibility has not been fully investigated.

How the NCS will address the problem The NCS will include collection of specimens that will allow assessment of exposure to pesticides *in utero* and postnatally, and will include neurobehavioral and cognitive examinations during infancy and later in childhood. These examinations will be designed to assess those aspects of neurobehavior and cognition most likely to be affected by pesticides (see Amler comments in Goldman, 2000 [neurotoxicology]). Linkage to school records may also allow for indirect assessment of cognitive function. Appropriate samples for characterization of the paraoxonase gene, and plasma for characterization of paraoxonase activity, will also be needed (Furlong et al., 2002).

If agents or use patterns thereof can be identified that have adverse effects on children regulations could be changed to reduce exposure to levels to those found to be safe in the NCS.

Sample size considerations: We assume that the frequency of detectable exposure is low; for example, one study (Whyatt et al., in press, Environ Health Perspect) suggests that 1% of pregnant women have detectable levels in plasma of methyl parathion, an organophosphate pesticide. With 100,000 subjects taking an IQ-type test, we would be able to detect an IQ decrement in the exposed group of about 1.5 points (where population mean is 100).

4. Hypothesis Prenatal infection and mediators of inflammation are risk factors for neurodevelopmental disabilities, such as cerebral palsy and autism.

Magnitude of the Problem Cerebral palsy affects approximately 0.2% of children (Kuban and Levitan, 1994), and autism affects about 0.3% (Yeargin-Allsopp, 2003). The prevalence of cerebral palsy in the United States is increasing, due to the increased survival of very low and low birthweight infants (Bhushan et al., 1993). Whether the frequency of autism is increasing is controversial, because recent estimates of higher prevalence may be due to inclusion of less severe cases. These relatively rare developmental disabilities have a devastating effect on the lives of the affected persons and their families. While estimates vary, the annual costs for cerebral palsy are about $17.2 billion and for autism are about $7.6 billion (Landrigan et al., 2002).

State of the Science Exposure to prenatal infection or mediators of inflammation may increase risk of cerebral palsy (Nelson, 2002). In term pregnancies, about 1-2% are affected by chorioamnionitis (intrauterine infection); in pregnancies ending in preterm births, the prevalence of such infection is higher (Wu and Colford, 2000). Fetal inflammatory response to intrauterine infection includes increased levels of fetal cytokines; such cytokines can be neurotoxic (Yoon, 1998; Dammann and Leviton, 1998). About one half of all cases of cerebral palsy occur in children born at term; only two small studies of chorioamnionitis and cerebral palsy among children born at term have been done (Grether and Nelson, 1997; Nelson and Ellenberg, 1985). About 20% of cerebral palsy may be due to chorioamnionitis (Wu and Colford, 2000).

While there are some data on the relation of viral infections in pregnancy to occurrence of autism, few causal agents have been established—rubella being one (Rodier and Hyman, 1998). The more general relation of prenatal infection, such as chorioamnionitis, and of exposure to mediators of inflammation to risk, as has been examined for cerebral palsy, to our knowledge, has not been studied in relation to autism. Such studies are overdue because of the role immune abnormalities may play in autism and the increased knowledge of the neurotoxicity of inflammatory cytokines (Horning and Lipkin, 2001). Although a large portion of autism may be genetically determined, the inherited predisposition may increase susceptibility to infection or inflammatory-induced disease.

How the NCS will address the problem A thorough assessment of prenatal infection and exposure to mediators of infection will be part of the NCS. Histologic confirmation of chorioamnionitis will require pathologic and microbiologic evaluation of placentas. Assessment of the neurodevopment of children will need to include diagnostic algorithms that identify all cases of cerebral palsy and autism spectrum disorder. In addition, linkage to physician or school records may help identify some cases of these disorders. Improved understanding of the role that prenatal infection and mediators of inflammation play in the etiology of these developmental disabilities will help guide design of clinical trials designed to reduce exposure to these agents.

Sample size considerations Assuming 100,000 infants born into the study, with an exposure prevalence of 2%, the smallest detectable relative risk would be, for cerebral palsy, 2.8; and for autism, would be 2.4.

5. Hypothesis Infection and mediators of inflammation during pregnancy and the perinatal period are associated with increased risk of schizophrenia

Magnitude of the Problem By age 21, approximately 0.3% of the population develops schizophrenia (Bresnahan et al., 2000), and thereafter the cumulative incidence increases to about twice that (Kendler, 1996). The annual cost of schizophrenia in the United States was recently estimated at $65.2 billion (Cuffel et al., 1996), and a substantial portion is due to disease in young adults (Genduso and Haley, 1997). About two thirds of those who develop schizophrenia continue to be affected throughout adult life (Bromet and Fenning, 1999).

State of the Science While infectious agents have been suspected of increasing risk of schizophrenia, their role has not been established (Bromet and Fenning, 1999; Buka et al., 2001). In recent data from long term follow-up of participants in the US Collaborative Perinatal Project (an NCS-like longitudinal study performed in the US in the 1960s) levels of maternal pregnancy serum immunoglobulins (IgG and IgM) were associated with increased risk of schizophrenia in offspring, suggesting that maternal infection increased the risk of schizophrenia among children from those pregnancies (Buka et al., 2001a). Evidence that increased exposure to mediators of inflammation *in utero* is associated with higher risk of schizophrenia has also been reported (Buka et al., 2001b).

Furthermore, levels of specific antibodies were examined for a variety of infectious agents and only elevations of antiobodies to herpes simplex virus, type 2 (genital herpes), were associated with increased risk of schizophrenia (Buka et al., 2001a). Herpes simplex viruses are known to cause encephalitis in infants (Corey, 1989), thus latent effects of less severe infection are biologically plausible. Investigation into effects of early exposure to herpes simplex type 2 is timely given the recent increase in prevalence of infection among young adults in the United States, where over 20% of the population aged 12 or more years is now seropositive (Xu, 2002). While other infectious agents are also suspected of increasing risk, the data for herpes provides a specific example for investigation.

How the NCS will address the problem Another look at the relation between maternal infection, and in particular with herpes simplex type 2, and risk of schizophrenia is needed. While a simple examination of maternal antibody titers would advance the science in this area, consideration of the timing of the infection in relation to birth would be useful, which would require multiple blood samples during pregnancy. Collection of swabs of the lesions for viral culture would enable an evaluation of the timing and rate of viral shedding in relation to subsequent schizophrenia. In addition, ascertainment of schizophrenia among children born into the NCS could rely on reports of clinical diagnosis, or, for a more sensitive assessment of outcome, could employ screening questionnaires aimed at identifying subjects with lesser degrees of illness, that would be more completely defined in targeted follow-up of those who were screen-positive.
If prenatal exposure to herpes simplex type 2 infection is associated with schizophrenia, management of active disease in pregnancy with antiviral chemotherapy may be

worthwhile. Furthermore, preventive measures, based on partner screening and barrier contraceptive methods during pregnancy, may help reduce the burden of this disease.

Sample size considerations: Assuming 100,000 children are followed to age 21, and an exposure prevalence of 10% (e.g., for herpes simplex type 2), the smallest detectable relative risk is 1.6.

6. Hypothesis: Exposures early in life that lead to neurotoxic effects are associated with increased risk of injury.

Magnitude of the problem: Magnitude of the problem: Injuries are the leading cause of death in children and adolescents after the first year of life. Every year between 20-25 percent of all children sustain an injury severe enough to require medical attention, missed school, and/or bed rest (CDC, NCIPC, Childhood Injury Fact Sheet, www.cdc.gov/ncipc/factsheets/childh.htm).

State of the science: A variety of environmental exposures are related to neuropsychological deficits (Mendola, et al. 2002). Exposure to lead, a classic neurotoxicant, has been associated with increased aggression and delinquency (Needleman, et al. 1996; Needleman, et al. 2002). Children with prenatal alcohol exposure, another known neurotoxicant, exhibit problem behaviors such as hyperactivity, impulsivity, poor socialization skills and deficits in executive functioning (Mattson, et al. 2001).

Important risk factors for childhood injuries include age, sex, behavioral characteristics of the child, family background, and use of drugs and alcohol.
The behavioral effects of neurotoxicant exposure may predispose children to injury because they fail to recognize and appropriately respond to hazards or because their resulting aggressive or antisocial behaviors are more likely to place them in harms way. Other social and environmental factors, such as neighborhood safety and caregiver supervision may mitigate these effects. Most suspected neurotoxicants have not been evaluated for their long-term impact on child development and potential injury risk and potential protective factors that might mitigate risk have received little attention.

How the NCS will address the problem The NCS will expend a substantial effort in early years to assess child development and factors that may be harmful (potential neurotoxic exposures) as well as helpful (caregiver supervision) to development. This hypothesis takes advantage of those measurements to address another set of endpoints related to child injuries, a substantial public health concern. The physical, mental and emotional development of the child can play a large role in injury risk. Despite the impact of child injuries, there is not a standard system to enumerate these events. The NCS can establish routine data capture of injury events that require medical care and may routinely survey parents regarding less serious injuries treated at home.

7. The original hypothesis in this position – "Attributes of child care and a child's relationship with caregivers influence risk of injury" - was intended as a placeholder while awaiting additional input from the Injury Working Group and other sources. To date, insufficient evidence has been found to support that hypothesis.

8. Hypothesis: Repeated head trauma has a cumulative adverse effect on neurocognitive development.

Magnitude of the problem: Traumatic brain injury (TBI) is associated with deleterious changes in behavioural, neurologic, and developmental measures for even mild to moderate injury (Hawley, et al. 2002; Anderson, et al. 2001). The precise incidence of childhood TBI in the US is difficult to pinpoint due to variations in reporting by severity of injury; in 1995-96, there was an annual average of approximately 7 emergency department visits for TBI per 1,000 children <15 years of age. The incidence of repeat or repeated head trauma among children is not known, though people with at least one TBI are at increased risk of subsequent injury (Salcido and Costich 1992).

State of the science: Head trauma, even mild head trauma, in close temporal sequence to an initial episode of TBI is associated with a seemingly disproportionate degree of morbidity and mortality (Cantu 1998). Though the mechanism behind "second impact syndrome" is not well-understood, it raises questions about cumulative effects of recurrent mild head trauma among children. Though the classic setting for repeat TBI is athletic competition (e.g., an estimated 20% of high school football players sustain at least one concussion each season (Kelly and Rosenberg 1998)), normal activities of childhood also provide ample opportunity for repetitive mild head trauma.

How the NCS will address the problem: Within the NCS, information on TBI of varying severity can be obtained from interview and medical records, at a minimum, in addition to data on activity in general and participation in sports. Behavioural, neurologic, and development outcomes will be assessed through interviews, examinations, and linkage to other data systems such as medical records and, potentially, school records.

Introduction to asthma-related hypotheses, #'s 9 – 14

Magnitude of the problem: Almost 6% of US children younger than 18 years of age (approximately 4 million children altogether) report having had an asthma attack within the last year (Akinbami and Schoendorf 2002). Asthma is associated with substantial physical and behavioural disability among children; 30% of children with asthma have reported activity limitation, compared to 5% of children without asthma. In addition, asthma was estimated to have accounted for an additional 10 million missed school days and 13 million physician contacts among children in 1988 (Taylor and Newacheck 1992), an underestimate of the current burden, given increasing trends in asthma prevalence and associated morbidity (Mannino, et al. 2002). Asthma prevalence among children almost doubled from 1980-1995. The annual estimated cost of pediatric asthma in the US in 1997 was $6.6 billion (Landrigan 2002).

State of the science: Asthma is a complex disease characterized by pulmonary obstruction due to inflammatory response within central and peripheral airways. Asthma is considered to have a variety of clinical phenotypes, carrying implications for disease etiology, evolution, and severity (Martinez and Helms 1998; Martinez 2002). Current understanding of the etiology and severity of asthma focuses on individual response to a wide range of immunogenic and immuno-protective factors (Busse and Lemanske 2001). This focus opens a wide range of potential research areas addressing interactions between host response (e.g., individual inflammatory response, genetic make-up), potential inflammatory triggers (e.g., ozone, particulate matter, and other airborne pollutants; viral infection; animal or fungal antigens), and potential protective factors (e.g., early exposure to bacterial endotoxin, dietary antioxidants). The following six sections address the specific NCS research questions related to asthma in more detail.

Several of the hypotheses (i.e., #s 10, 11, 13) address the possible influence of fetal or early life exposures on subsequent risk of asthma. Though the nature and timing of those exposures vary, the proposed final pathway resulting in increased risk of asthma may be similar, focusing on the immunologic underpinnings of asthma. Specifically, as each hypothesis briefly outlines, each set of exposures has a potential influence on the developing immune system's maturation from the initial (e.g., fetal, early life) predominance of Type 2 (Th2) response to allergic insult to a predominantly Type 1 (Th1) response. The elaboration of each specific hypotheses below briefly addresses the particular manner in which the potential exposure(s) influence early development of a child's lymphocytic response to allergenic stimulation.

How the NCS will address the problem: The NCS will collect a variety of data useful for characterizing asthma. Interview data will assess a history of relevant symptoms, as well as physician diagnosis and health care use. In addition, the NCS may allow for linkage to medical or pharmacy records. At a minimum, non-invasive diagnostic tests such as peak flow monitoring or perhaps pulmonary function tests will be performed for at least a subset of the NCS population.

Sample size considerations for the asthma hypotheses The following power estimate assumes a sample size of 100,000 at age of diagnosis, an asthma incidence of 5%, and a cut-off value for "high" exposure based on the upper 5th percentile of NCS subjects (i.e., a proportion exposed of 0.05). It assumes only a main effects model based on exposure to a single factor (e.g., a single air pollutant) without consideration of interactions with other exposures, genetic factors or family history, etc. Under those assumptions, the smallest detectable relative risk is approximately 1.2.

9. Hypothesis: Exposure to indoor and outdoor air pollution and bioaerosols (including allergens, endotoxin, and mold) is associated with increased risk of asthma.

State of the science: There is clear evidence that air pollutants, particularly ozone and some constituents of particulate matter, as well as transition metals, diesel exhaust, and biologicals such as endotoxin can exacerbate existing asthma, but the role of these air contaminants in the induction of asthma is less clear (Peden, 2002). There is some evidence that dust mite and cockroach allergens, as well as environmental tobacco smoke can cause asthma, but more research is needed to examine a variety of airborne exposures early in life, including prenatal exposures, in order to identify factors related to the onset of asthma (Redd, 2002).

Exposure to air pollution and the resulting inflammation has generally been thought to precede the changes in airway morphology associated with asthma and to be a relatively minor contributor to the incidence of asthma. However, it appears that lung development may be altered in parallel with inflammation, causing structural changes in airways years before the clinical expression of asthma (Parnia, et al. 2002).
Many theories of asthma induction are based on immune response to allergic or irritant inflammation. These responses are complex and dependent on a variety of factors including genetics, prior exposures (sensitization, infections, etc.), and timing of exposures relative to immune system development. For example, early exposure to pets and farm animals has been found to be protective for allergic sensitization (Gehring et al. 2002) and later exposure to pets increase risk for asthma (McConnell et al., 2002). A longitudinal study of wheezing in young children found total house dust endotoxin increased risk, but pets in the home decreased risk (Litonjua, et al. 2002).

How the NCS will address the problem Since exposure to endotoxin, allergens and air pollutants are ubiquitous and the impact of various potential combinations of exposures and susceptibilities are poorly understood, this question is ideally suited for the NCS. Estimation of exposure to specific air pollutants likely will be derived from existing air quality monitors; air sampling in and around participants' residences and schools; activity diaries or measurements; and possibly personal air samplers for subsets of the study population. Exposure to indoor allergens and endotoxin will be estimated from residential and school environmental samples, as well as from information obtained by history (e.g., pet ownership).

10. Hypothesis: Respiratory viral infection early in life is associated with increased risk of asthma.

State of the science: Respiratory tract infections have been linked with asthma for over 40 years, but the recent literature reflects the complex nature of this relationship. While some studies have suggested that early life infections protect against the development of allergy and asthma, others suggest that viral infections may promote allergic sensitization and the development of asthma (Mallia, et al. 2002).

Factors such as family size, particularly the presence of older siblings, and daycare attendance have been found to be protective (Ball, et al., 2000; Kramer, et al., 1999). Both older siblings and daycare serve as proxy measures of increased prevalence of early infections. The protective mechanism has been assumed to be stimulation of the infant's development of type 1 immune response (IgG and IgM production) moving away from a type 2 response (IgE production and an allergic profile of lymphocytes). Reduced frequency of infection, particularly among genetically susceptible infants with impaired type 1 immunity, could lead to increased risk for allergic diseases including asthma.

On the other hand, studies that have actually measured infectious episodes (either by parental report or physician records) have found the opposite effect. The number and severity of respiratory tract infections early in life appear to increase the risk for asthma (Ponsonby, et al. 1999; Castro-Rodriguez, et al. 1999). Early infections, particularly with respiratory syncytial virus, have been associated with wheezing and subsequent asthma. However, it is unclear whether these infections actively induce asthma or simply precipitate symptomatic asthma among a sub-group of children who were going to develop asthma later in life regardless of early infection. These relations are further complicated by interactions between viral infections and allergic sensitization, age and airway size, as well as exposure to environmental tobacco smoke and other factors.

How the NCS will address the problem: Exposure to infection and related inflammation both *in utero* and after birth is the basis of several hypotheses in addition to this one (e.g., see Hypothesis #s 2, 4, 5). Relevant maternal and feto- infant (e.g., cord blood) samples will be taken to assess those exposures. In addition, infant and childhood exposure to infections (including proxy measures as described above) will be ascertained by interview and potentially by linkage to medical records. In addition, biologic samples for characterization of immune response and genetically determined inflammatory factors will be collected.

11. Hypothesis: Maternal stress during pregnancy is associated with increased risk of asthma.

State of the science: A key factor in the development of asthma is thought to be the ability of the child's immune system to move from a primarily type 2 response to a type 1 response early in life. In addition to other factors that can impact this migration, such as infections, maternal stress responses might impact the developing immune system *in utero*. In particular, elevations in stress-induced maternal cortisol levels may impact the fetal immune system and lead to an increased risk of atopic diseases in genetically susceptible children (von Hertzen, 2002).

Glucocorticosteriods appear to drive the Th1/Th2 balance toward a Th2 cytokine profile as do cathecolamines (Elenkov, 1999). Placental corticotropin-releasing hormone is stimulated by maternal cortisol creating a positive feedback loop that increases both maternal and fetal cortisol. Maternal cortisol also crosses the placenta and while most is metabolized before reaching the fetus, the remainder is thought to be sufficient to have a major effect on fetal cortisol concentrations, furthering the differentiation of T-helper cell phenotypes and the persistence of a predominantly Th2-type lymphocyte response. Additionally, increases in maternal stress may be related to behavioral characteristics (such as smoking) that will increase subsequent asthma risk.

How the NCS will address the problem Maternal stress will be assessed by physiologic measures (e.g., serum or salivary cortisol levels) and interview instruments. Since stress during pregnancy may be associated with preterm birth, lower birth weight and other adverse outcomes of pregnancy, careful consideration of multiple confounders is needed to evaluate the influence of maternal stress during pregnancy on the developing immune system and risk of asthma. Biologic samples for the assessment of immune response will be collected for this and other related hypotheses.

12. Hypothesis: Antioxidant constituents of diet decrease risk of asthma

State of the science: Interest in the relation between dietary antioxidant consumption and risk of asthma arises from several directions. First, general population-based health surveys have demonstrated modest direct associations between pulmonary function and antioxidant consumption and serum levels (Schunemann, et al. 2002; Schwartz and Weiss 1990). Second, markers of oxidative damage are found at higher concentrations in the exhaled breath condensate of children with asthma compared to those without asthma, while markers of antioxidant status are higher among children without asthma (Corradi, et al. 2002). Third, the deleterious pulmonary response to ozone exposure is somewhat modified by oral administration of Vitamins C and E (Samet, et al. 2001; Romieu, et al. 1998). Pulmonary inflammatory response to ozone exposure is thought to be mediated at least in part by oxidative damage to airway tissues.

Little direct evidence exists, however, concerning the relationship between antioxidant consumption or serum levels and the development of asthma, especially in relation to exposure to potential oxidative stressors such as ozone, nitrous oxides, or environmental tobacco smoke. In addition, examination of the temporal relationship between antioxidant consumption on subsequent outcome and assessment of genetic variation in immunologic response to oxidative stress and the potential modifying influence of antioxidant exposure will be important in understanding potential intervention techniques, whether related to asthma incidence or treatment.

How the NCS will address the problem Antioxidant consumption will be measured by dietary assessment (e.g., recall, diary) as best suited for this and other hypotheses. Antioxidant levels can be assessed through serum samples and possibly other biologic measures (e.g., exhaled breath condensate). Samples enabling assessment of systemic measures of oxidative stress, such as urinary isoprotanes, will also be obtained.

13. Hypothesis: Early exposure to bacterial and microbial product decreases risk of asthma (hygiene hypothesis).

State of the science: Starting in the late 1980's a number of papers suggested that "… allergic diseases were prevented by infection in early childhood …", an hypothesis running counter to observations that infection is generally an allergenic stimulus (Strachan 2000). Initial investigations focused on epidemiologic associations between family size, birth order, and attendance in daycare on the risk of asthma and other allergic disorders. Subsequent investigation has examined immunologic profiles of people with and without asthma, as well as patterns of early infection and exposure to bacterial endotoxin among children with and without asthma (Braun-Fahrländer, et al. 2002).

General findings from these studies can be interpreted to suggest that asthma is associated with a failure of the immune system to develop normally. This lack of immunologic maturity may be associated with decreased early life exposure to certain infections (e.g., M. tuberculosis, measles, Hepatitis A) or microbial products in general (e.g., bacterial endotoxin) that directly stimulate the Th-1 lymphocyte response. Attenuation of the normal change from a predominantly Th-2 lymphocyte response to stimuli, associated with allergic inflammation, to a balanced response between Th-1 (associated with cellular defense) and Th-2 lymphocytes has been postulated as a potential mechanism for increased asthma risk (Busse and Lemanske 2001; Kheradmand, et al 2002). The degree to which asthma etiology can be directly related to decreased exposure to certain infections or microbial products; the necessary timing of these exposures to initiate optimal immune response throughout life (or, whether the immunologic response is programmed *in utero* [Warner 1998]); and individual variation in response to early infections are in need of additional in-depth investigation to further development of asthma prevention and treatment strategies.

How the NCS will address the problem: Early exposure to infection and potential allergens will be assessed by interview history (e.g., family structure, illness, daycare attendance, pet ownership). Household environmental samples will be used to assess exposure to endotoxin and potential allergens.

14. Hypothesis: Access to health care and management of asthma are strongly related to risk of asthma. (Note: The wording of this hypothesis has been changed to reflect the belated recognition that, due to the rarity of the outcome, asthma mortality is not an appropriate outcome for the NCS. Further development of support for this hypothesis will benefit from additional input from the Health Services and Asthma Working Groups.)

State of the science: The beneficial effect of appropriate health care on morbidity associated with asthma is well known (Greineder, et al. 1995; Homer, et al. 1996). However, the relationship between receipt of health care, particularly early in life, and subsequent development of asthma is not known. Receipt of appropriate services early in life may lead to decreased exposure to asthma triggers, such as environmental tobacco smoke or animal dander, that have been associated both with asthma incidence and severity.

Alternatively, health care received early in life is likely associated with increased use of antibiotics. The results of some studies suggest that early use of antibiotics may be associated with an increased risk of subsequent asthma, either by curtailing normal immune response to infection or by causing alterations in bacterial flora that then influence the individual's immune response (Mattes and Karmaus 1999). Disentangling the interactions between beneficial effects of health care, early exposure to viral infections, early exposure to bacterial infections, and the use of antibiotics associated with health care on asthma induction is necessary to gain more complete understanding of the influence of health care on childhood asthma.

Introduction to obesity and insulin resistance-related hypotheses, #'s 15-20

Magnitude of the Problem The prevalence of overweight among children is greater than 15% among children aged 6 years or more, and this prevalence has increased over the past 40 years (Ogden, 2002, Kuczmarski, 1994). Being overweight as a child is a risk factor for being overweight in adulthood (Serdula et al. 1993), and is associated with increased risk of type 2 diabetes, hypertension, and coronary artery disease (Freedman et al. 2001). Furthermore, being overweight as a child increases the risk of developing type 2 diabetes before the age of 21 years (Sinha et al. 2002). Because child overweight is a risk factor for adult overweight, child overweight contributes to the more than $40 billion annual cost of obesity in the United States (Colditz 1992).

The present best estimate of the prevalence of type 2 diabetes among those less than age 21 years in the U.S. is about 0.1%, based on NHANES data from 1988-1994 (Fagot-Campagna et al. 2001). Given the increase in overweight among children, it seems reasonable to assume that the prevalence now is higher than 0.1%--but by how much is unclear. Thus, type 2 diabetes may not be common enough for the NCS to examine with sufficient power. Nonetheless, insulin resistance, or closely-related conditions such as metabolic syndrome, are outcomes that would occur with sufficient frequency among subjects less than aged 21 years that they could serve as outcomes. Insulin resistance is considered the underlying abnormality in metabolic syndrome. Metabolic syndrome, according to the World Health Organization (1998) and as modified by Laaksonen et al. (2002), is defined by: fasting hyperinsulinemia, impaired fasting glycemia or diabetes, and the presence of at least two of the following: abdominal obesity, dislipidemia (hypertriglyceridemia or low HDL cholesterol), or hypertension. Such a definition is feasible for large-scale epidemiologic studies, and identifies those who are at high risk of developing type 2 diabetes. The prevalence of metabolic syndrome among adults, as compared with the prevalence of type 2 diabetes, is about 4-fold higher (Laaksonen et al. 2002). Thus, it is reasonable to assume that an outcome definition of metabolic syndrome like that presented above would have a prevalence above 0.2%, meaning that the NCS would have sufficient power to examine it for a wide range of exposure prevalences.

15. Hypothesis Impaired maternal glucose metabolism during pregnancy is directly related to risk of obesity and insulin resistance in offspring.

Magnitude of the Problem See previous discussion, above.

State of the Science The offspring of mothers who have type 1 diabetes are at increased risk of overweight, and this effect is often evident as early as 4 years of age (Whitaker and Dietz, 1998). Other studies, where mothers with gestational diabetes were grouped together with type 1 and type 2 diabetics, have also shown increased risk of overweight in offspring (Whitaker and Dietz, 1998). On the basis of these observations, offspring of mothers with gestational diabetes, or lesser degrees of impaired glucose metabolism, are suspected of being at increased risk of obesity, but there are few data available to address the issue, and those data that are available had extremely limited statistical power (Whitaker and Dietz 1998; Dabelea and Pettitt 2001)

Whether impaired maternal glucose metabolism during pregnancy causes overweight in children is an especially timely issue because the prevalence of overweight among women of childbearing age has increased (Mokdad, et al, 1999), and overweight is a risk factor for impaired maternal glucose metabolism and gestational diabetes (Kjos and Buchanan, 1999).

How the NCS will address the problem The NCS will include a standardized assessment of glucose tolerance during pregnancy, and will assess body size and habitus in offspring multiple times during childhood and adolescence. At least once before age 21, a fasting blood sample and blood pressure measurement would be required to make the diagnosis of metabolic syndrome.

If the NCS results indicate that impaired glucose metabolism during pregnancy increases risk of overweight and insulin resistance in offspring, increased emphasis could be placed on the importance of weight control before pregnancy, and for greater glucose control during pregnancy, even among those without clinical gestational diabetes (if results support that).

Sample size considerations: About 4-7% of pregnancies are complicated by gestational diabetes (Kjos and Buchanan 1999). Assuming 100,000 children, and an exposure prevalence of 5%, the smallest detectable relative risk for obesity (prevalence 10%, using 30 kg/m2 definition) would be about 1.2; the smallest detectable relative risk for metabolic syndrome (assumed prevalence 0.4%) would be 1.7.

16. Hypothesis Intrauterine growth restriction as determined by serial ultrasound examination is associated with subsequent risk of central obesity and insulin resistance in offspring, independent of subsequent body mass index.

State of the Science Birth weight has been inversely associated fairly consistently with increased body mass index later in life, although whether this association is causal remains controversial (Joseph and Kramer 1996). The relation of birth weight to central obesity, conditional on body mass index, however, has been investigated in only a few small studies (Ong et al., 2000; Garnett et al., 2001); these studies support an inverse association. Although birth weight does not make an important contribution to the population attributable risk of cardiovascular disease (Maher Rasmussen, 2001), this contribution may have been underestimated because birth weight is a poor proxy for the intrauterine events that are related to subsequent risk of obesity, central obesity, and cardiovascular disease. An improved assessment of these intrauterine events can be provided by serial ultrasound examinations during pregnancy (Ott, 1997).

An improved understanding of the relation between fetal growth, child growth, and subsequent risks of chronic disease will help target and prioritize research on the proximal causes of fetal and child growth. If, for example, the relation of fetal growth to subsequent risk of chronic disease is much greater than previously recognized, addressing the current paucity of data on determinants of fetal growth will require high priority.

How the NCS will address the problem The NCS will include both serial ultrasound examinations during pregnancy and assessments of central obesity at several ages. Assessment of central obesity for a large number of subjects could be based on abdominal girth measurements. The relation of abdominal girth to central adiposity could be calibrated in a substudy of the NCS, or in external studies. At least once before age 21, a fasting blood sample and blood pressure measurement would be required to make the diagnosis of metabolic syndrome

Sample size considerations Using the assumed prevalence of metabolic syndrome as a starting point (0.4%) and estimating that approximately 10% of the study population will have sub-optimal fetal growth, the smallest detectable relative risk in a population of 100,000 is 1.5.

17. Hypothesis Breast milk feeding, compared with infant formula feeding, and breastfeeding duration are associated with lower rates of obesity and lower risk of insulin resistance.

Magnitude of the Problem See previous discussion, above.

State of the Science Although the relation of breastfeeding to subsequent overweight has been examined numerous times (Parsons, 1999), only the results of two large, recent studies have provided evidence that there may be a protective effect (Gillman, 2001; von Kries, 1999). Data remain sparse on whether the protective association with overweight persists later in adolescence (Gillman, 2001). Furthermore, questions remain whether the protective effect, if any, is due to constituents of breast milk, or due to differences in feeding practices for breast and formula-fed infants. The existing studies relied on retrospectively-reported breastfeeding histories, which provide reasonably good information; nonetheless, prospectively collected data stand to improve assessment of breast feeding and allow more accurate estimates of the association.

If breastfeeding does help prevent subsequent obesity, this would be one of the few protective preventive measures available (Dietz, 2001). The relationship of large racial and ethnic differences in infant feeding practices (e.g., approximately 34% of white infants are breastfed at 6 months of age, compared to 21% of black children and 28% of Hispanic children [US Department of Health and Human Services 2002]) to subsequent differences in childhood obesity (Ogden, et al., 2002) may also be explored. Furthermore, by identifying whether the protective effect is due to constituents of breast milk or to differences in feeding practices would help inform recommendations regarding mode of breast milk feeding in infants.

How the NCS will address the problem The NCS will collect information about breastfeeding practices and will obtain one or more specimen(s) of breast milk during infancy. In addition, as noted above, the NCS will assess body size in offspring multiple times during childhood and adolescence, and will assess the prevalence of metabolic syndrome at least once.

Sample size considerations In 2000, almost 70% of all infants were breastfed (either exclusively or in combination with formula feeding) before initial hospital discharge. However, by 6 months of age, just under one-third of infants were breastfed (US Department of Health and Human Services 2002). Assuming a breastfeeding prevalence of 50% (in line with estimates from NHANES III [Hediger et al., 2001]), and using the power assumptions noted above, the smallest detectable relative risk for obesity would be 1.05; and for metabolic syndrome would be 1.3.

18. Hypothesis Dietary predictors of obesity and insulin resistance include reduced intake of fiber and whole grains, and high glycemic index.

Magnitude of the Problem See previous discussion, above.

State of the Science The glycemic index of foods reflects the increase in blood sugar that occurs after feeding; whole grain and high fiber foods tend to have a low glycemic index. Animal and adult human data suggest that a diet rich in foods with a low glycemic index prevents obesity. Furthermore, consumption of foods with a high glycemic index has been associated with increased risk of type 2 diabetes in some epidemiologic studies of adults, but not all (Jenkins et al., 2002). The data for humans, while sparse (Jenkins et al., 2002), are nonetheless sufficient, when considered with the supporting mechanistic evidence (Ludwig, 2002), to support the need for randomized trials to evaluate efficacy of diets with low glycemic indexes for prevention of obesity in adults (Brand-Miller et al., 2002). Meals with a high glycemic index were found to induce metabolic responses that promote food intake in teenage boys, suggesting that further work on glycemic index and obesity in children is needed (Ludwig et al., 1999). Given the paucity of human data, and the relation between childhood and adult obesity, further data on this aspect of diet in relation to childhood overweight is needed. If the NCS identifies attributes of diet that are associated with prevention of overweight in children, this could have a substantial impact on dietary recommendations.

How the NCS will address the problem The NCS will assess dietary intake of children at those ages where measurement is most accurate. As noted above, body habitus will be assessed numerous times throughout the study. At least once before age 21, a fasting blood sample and blood pressure measurement would be required to make the diagnosis of metabolic syndrome.

19. Hypothesis Environmental factors such as distance to parks, availability of walking routes in the neighborhood, and neighborhood safety are associated with risk of obesity and insulin resistance.

Magnitude of the Problem See previous discussion, above.

State of the Science The "built environment" comprises urban design, land use, and the transportation system, and encompasses patterns of human activity within the physical environment (Handy et al., 2002). The relation between the built environment, physical activity, and risk of obesity and insulin resistance needs further investigation (Handy et al., 2002). Factors that would enhance the assessment of the built environment in relation to physical activity and overweight are improved conceptual and statistical models, improved measures of aspects of the built environment that influence physical activity, and improved assessment of physical activity, relative to earlier work in the field. Improvement of measures of aspects of the built environment that influence physical activities relies in part on better identification of the relevant aspects of the built environment. Traditional measures of the built environment include density of people or jobs per unit area, land use mix, connectivity of streets, street scale, aesthetic qualities, and regional structure (Handy et al. 2002).

An improved understanding of the attributes of the built environment that influence physical activity and overweight will assist planners in the design and management of the built environment to promote public health.

How the NCS will address the problem The characteristics of the built environment for each subject in the study will be assessed (Weich et al., 2001). Physical activity will be assessed by interview, activity diary, and potentially by physiologic measurement. Height, weight, waist-to-hip ratio, and other indications of body habitus will be assessed, as noted for other hypotheses for this priority outcome.

Sample size considerations: As an example power calculation for this general hypothesis, the smallest detectable relative risk for metabolic syndrome in relation to presence of sidewalks in one's neighborhood (about 40% of people in the U.S. do not have sidewalks in their neighborhood [Brownson et al., 2001]), is approximately 1.4.

20. Hypothesis Social, behavioral, and family factors that affect development of dietary preferences and physical activity patterns early in childhood determine risk of childhood obesity and insulin resistance.

Magnitude of the Problem See previous discussion, above.

State of the Science While the importance of physical activity and energy balance (diet) in prevention of childhood overweight are well understood, the determinants of physical activity behaviors and dietary preferences need further research. Examples of research needs for physical activity behaviors are determinants of time spent outdoors (besides season), time watching television, and concerns about outdoorsafety (Kohl and Hobbs 1998). Furthermore, the effect of attitudes about physical activity, the effect of peer influence, and sociocultural factors needs further study.
Similarly, much remains to be learned about how early experiences with food and eating affect the development of dietary preferences (Nicklas et al. 2001; Story 2002; Birch and Fisher 1998).

Identifying familial and child-rearing practices that favor the adoption of healthy dietary and physical activity behaviours have the potential to yield specific interventions leading to the prevention of overweight and associated morbidity.

How the NCS will address the problem: Physical activity and diet assessments especially designed for children will be administered, either to parents or children, depending on age. Children's age has a large effect on the validity of the instruments measuring diet and physical activity. In addition, assessment of parental dietary and activity practices may be necessary to understand their influence on the acquisition of practices among their children. Child-care and school influences will also need to be evaluated. As noted above, body habitus will be assessed numerous times throughout the study. At least once before age 21, a fasting blood sample and blood pressure measurement would be required to make the diagnosis of metabolic syndrome.

21. Hypothesis *In utero* and subsequent exposure to environmental agents that affect the endocrine system (e.g., bisphenol A, atrazine, and lead) results in altered age at puberty.

Magnitude of the Problem A trend towards decreasing age at menarche in the U.S. has been reported (Kaplowitz et al. 2001), although some critics disagree (Lee et al. 2001; Viner 2002). Even if the trend has not been established, documented exposure of children and pregnant women to compounds carrying potential reproductive toxicity, as described below, support the importance of studying environmental determinants of age at puberty.

State of the Science Cross-sectional data from NHANES III (Wu, et al 2003) suggest that higher blood lead levels may be associated with a delay in onset of puberty. These results parallel similar findings in animals.

Bisphenol A is a high production volume chemical, used in a variety of applications including manufacturing of flame retardants, resins, and plastics. Bisphenol A is a weak estrogen (Pottenger et al., 2000). Human exposure may arise in a number of circumstances, for instance, when foods are contaminated by heated plastics. New data show that blood levels of bisphenol A in pregnant women (Schonfelder et al., 2002) are similar to those found in pregnant rats that give birth to offspring with bisphenol A-induced reproductive toxicity (Howdeschell et al, 1999; Rubin et al., 2001; Pottenger et al, 2000).

Atrazine is a widely used herbicide. In a population-based probability sample of children aged 3-13 years old, about 3% of children had detectable levels of an atrazine metabolite in their urine, and urban-rural differences in levels were not statistically significant. Recent experiments in peripubertal rats show that atrazine, in doses of 30 mg/kg orally, per day, for up to 25 days, delayed the onset of puberty (Ashby et al. 2002). Whether the doses effective in animal experiments result in urinary metabolite levels like those seen among children with detectable levels is not clear.

In the event that these exposures affect sexual maturation of children, exposures would need to be more tightly controlled or regulated.

How the NCS will address the problem Exposure to bisphenol A and atrazine can be assessed by measures of metabolite levels in urine; exposure to lead can be assessed by levels in whole blood. Pubertal development can be assessed by Tanner stages, and, for females, by ascertaining the age at which menstruation begins, and, for males, by ascertaining the presence of sperm in urine. The special significance of the NCS for the lead investigation is that prospective evaluations are needed. In the case of the other two exposures, human data are needed.

References

Akinbami LJ, Schoendorf KC. (2002). Trends in childhood asthma: prevalence, health care utilization, and mortality. Pediatrics 2002;110:313-22.

Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med. 1998 Jul;15(7):539-53.

Anderson VA, et al. (2001). Predictors of acute child and family outcome following traumatic brain injury in children. Pediatric Neurosurgery 2001;34:138-48.

Andrews WW, Hauth JC, Goldenberg RL. (2000). Infection and preterm birth. Am J Perinatol. 2000;17:357-65.

Ashby J, Tinwell H, Stevens J, Pastoor T, Breckenridge CB. The effects of atrazine on the sexual maturation of female rats. Regul Toxicol Pharmacol. 2002 Jun;35(3):468-73.

Ball, T.M. et al. Siblings day-care attendance, and the risk of asthma and wheezing during childhood. New England Journal of Medicine, 343:538-543 (2000).

Bhushan V, Paneth N, Kiely JL. Impact of improved survival of very low birth weight infants on recent secular trends in the prevalence of cerebral palsy. Pediatrics. 1993 Jun;91(6):1094-100

Birch LL, Fisher JO. Development of eating behaviors among children and adolescents. Pediatrics. 1998 Mar;101(3 Pt 2):539-49.

Brand-Miller JC, Holt SH, Pawlak DB, McMillan J. Glycemic index and obesity. Am J Clin Nutr. 2002 Jul;76(1):281S-5S.

Braun-Fahrländer C, etal. (2002). Environmental exposure to endotoxin and its relation to asthma in school-age children. New England Journal of Medicine 2002;347:869-77.

Bresnahan MA, Brown AS, Schaefer CA, Begg MD, Wyatt RJ, Susser ES. Incidence and cumulative risk of treated schizophrenia in the prenatal determinants of schizophrenia study. Schizophr Bull. 2000;26(2):297-308.

Brimijoin S, Koenigsberger C. Cholinesterases in neural development: new findings and toxicologic implications. Environ Health Perspect. 1999 Feb;107 Suppl 1:59-64

Bromet EJ, Fennig S. Epidemiology and natural history of schizophrenia. Biol Psychiatry. 1999 Oct 1;46(7):871-81

Brownson RC, Baker EA, Housemann RA, Brennan LK, Bacak SJ. Environmental and policy determinants of physical activity in the United States. Am J Public Health. 2001 Dec;91(12):1995-2003.

Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. Arch Gen Psychiatry. 2001a Nov;58(11):1032-7.

Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH. Maternal cytokine levels during pregnancy and adult psychosis. Brain Behav Immun. 2001b Dec;15(4):411-20.

Busse WW, Lemanske RF. (2001). Asthma. New England Journal of Medicine 2001;344:350-62.

Cantu RC. (1998). Second-impact syndrome. Clinics in Sports Medicine 1998;17:37-44. – Only have found (and read) abstract for this one

Castro-Rodriguez, J.A. et al. Association of radiologically ascertained pneumonia before age 3 yr with asthmalike symptoms and pulmonary function during childhood: a prospective study. American Journal of Respiratory Critical Care Medicine, 159:1891-1897 (1999).

Cherry N, Mackness M, Durrington P, Povey A, Dippnall M, Smith T, Mackness B. Paraoxonase (PON1) polymorphisms in farmers attributing ill health to sheep dip. Lancet. 2002 Mar 2;359(9308):763-4.

Colditz GA. Economic costs of obesity. American Journal of Clinical Nutrition. 55 (2): S503-S507 Suppl. S Feb 1992.

Corradi M, et al. (2002). Aldehydes and glutathione in exhaled breath condensate of children with asthma exacerbation. American Journal of Respiratory and Critical Care Medicine 2002 – currently as epub only.

Corey L, Whitley RJ, Stone EF, Mohan K. Difference between herpes simplex virus type 1 and type 2 neonatal encephalitis in neurological outcome. Lancet. 1988 Jan 2-9;1(8575-6):1-4.

Cuffel BJ, Jeste DV, Halpain M, Pratt C, Tarke H, Patterson TL. Treatment costs and use of community mental health services for schizophrenia by age cohorts. Am J Psychiatry. 1996 Jul;153(7):870-6.

Curl, CL, Fenske, RA, Elgethun, K. Organophosphorus pesticide exposure of urban and suburban pre-school children with organic and conventional diets. Environ Health Persp 2003, doi: 10.1289/ehp5754.

Currie KL, McDonald EC, Chung LT, Higgs AR. Concentrations of diazinon, chlorpyrifos, and bendiocarb after application in offices. Am Ind Hyg Assoc J. 1990 Jan;51(1):23-7.

Dabelea D, Pettitt DJ. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. J Pediatr Endocrinol Metab. 2001 Sep-Oct;14(8):1085-91.

Dammann O, Leviton A. Infection remote from the brain, neonatal white matter damage, and cerebral palsy in the preterm infant. Semin Pediatr Neurol. 1998 Sep;5(3):190-201

Dietz WH. Breastfeeding may help prevent childhood overweight. JAMA. 2001 May 16;285(19):2506-7.

Elenkov, I.J., et al. Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokinds and susceptibility to disease. Trends in Endocrinology and Metabolism, 10:359-368 (1999).

Eskenazi B, Bradman A, Castorina R. Exposures of children to organophosphate pesticides and their potential adverse health effects. Environ Health Perspect. 1999 Jun;107 Suppl 3:409-19.

Fagot-Campagna A, Saaddine JB, Flegal KM, Beckles GL. Diabetes, impaired fasting glucose, and elevated HbA1c in U.S. adolescents: the Third National Health and Nutrition Examination Survey. Diabetes Care. 2001 May;24(5):834-7.

Farrell T, Neale L, Cundy T. Congenital anomalies in the offspring of women with type 1, type 2 and gestational diabetes. Diabet Med. 2002 Apr;19(4):322-6

Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics. 2001 Sep;108(3):712-8

Furlong CE, Cole TB, Jarvik GP, Costa LG. Pharmacogenomic considerations of the paraoxonase polymorphisms. Pharmacogenomics. 2002 May;3(3):341-8

Garnett SP, Cowell CT, Baur LA, Fay RA, Lee J, Coakley J, Peat JK, Boulton TJ. Abdominal fat and birth size in healthy prepubertal children. Int J Obes Relat Metab Disord. 2001 Nov;25(11):1667-73.

Gehring U. et al. House dust endotoxin and allergic sensitization in children. American Journal of Respiratory Critical Care Medicine, 166:939-944 (2002).

Genduso LA, Haley JC. Cost of illness studies for schizophrenia: Components, benefits, results, and implications. American Journal of Managed Care
3 (6): 873-877 Jun 1997.

Gillman MW, Rifas-Shiman SL, Camargo CA Jr, Berkey CS, Frazier AL, Rockett HR, Field AE, Colditz GA. Risk of overweight among adolescents who were breastfed as infants. JAMA. 2001 May 16;285(19):2461-7.

Goldman LR, Bearer CF. Framing the problem of developmental neurotoxicology in children: Session VII summary and research needs. Neurotoxicology 2000;21(1-2):274-276.

Greineder DK, Loane KC, Parks P. Reduction in resource utilization by an asthma outreach program. Archives of Pediatric and Adolescent Medicine 1995;149;415-20.

Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birth weight. JAMA. 1997 Jul 16;278(3):207-11

Hack M, Flannery DJ, Klein N, et al. (2002). Outcomes in young adulthood for very-low-birth-weight infants. N Engl J Med. 2002;346:149-57.

Handy SL, Boarnet MG, Ewing R, Killingsworth RE. How the built environment affects physical activity: views from urban planning. Am J Prev Med. 2002 Aug;23(2 Suppl):64-73.

Hawley CA, et al. (2002). Children's brain injury: a postal follow-up of 525 children from one health region in the UK. Brain Injury 2002;16:969-85.

Hediger ML, Overpeck MD, Kuczmarski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. JAMA. 2001 May 16;285(19):2453-60.

Hill RH Jr, Head SL, Baker S, Gregg M, Shealy DB, Bailey SL, Williams CC, Sampson EJ, Needham LL. Pesticide residues in urine of adults living in the United States: reference range concentrations. Environ Res. 1995 Nov;71(2):99-108

Homer CJ, et al. (1996). Does quality of care affect rates of hospitalization for childhood asthma? Pediatrics 1996;98:18-23.

Howdeshell KL, Hotchkiss AK, Thayer KA, Vandenbergh JG, vom Saal FS. Exposure to bisphenol A advances puberty. Nature. 1999 Oct 21;401(6755):763-4.

Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol. 2002 Jun 19;39(12):1890-900

Horning M, Lipkin WI. MRDD Research Reviews 2001;200-210.

Jenkins DJ, Kendall CW, Augustin LS, Franceschi S, Hamidi M, Marchie A, Jenkins AL, Axelsen M. Glycemic index: overview of implications in health and disease. Am J Clin Nutr. 2002 Jul;76(1):266S-73S.

Joseph KS, Kramer MS. Review of the evidence on fetal and early childhood antecedents of adult chronic disease. Epidemiol Rev. 1996;18(2):158-74.

Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier onset of puberty in girls: relation to increased body mass index and race. Pediatrics. 2001 Aug;108(2):347-53.

Kelly JP, Rosenberg JH. (1998). The development of guidelines for the management of concussion in sports. Journal of Head Trauma and Rehabilitation 1998;13:53-65.

Kendler KS, Gallagher TJ, Abelson JM, Kessler RC. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. The National Comorbidity Survey. Arch Gen Psychiatry. 1996 Nov;53(11):1022-31

Kherdamand F, Rishi K, Corry DB. (2002). Environmental contributions to the asthma epidemic. Environmental Health Perspectives (2002);110(suppl 4):553-6.

Kjos SL, Buchanan TA. Gestational diabetes mellitus. N Engl J Med. 1999 Dec 2;341(23):1749-56

Kohl HW 3rd, Hobbs KE. Development of physical activity behaviors among children and adolescents. Pediatrics. 1998 Mar;101(3 Pt 2):549-54.

Kramer, U. et al. Age of entry to day nursery and allergy in later childhood. Lancet, 353:450-454 (1999).

Kuban KC, Leviton A. Cerebral palsy. N Engl J Med. 1994 Jan 20;330(3):188-95.

Kuczmarski RJ, Flegal KM, Campbell SM, Johnson CL. Increasing prevalence of overweight among US adults. The National Health and Nutrition Examination Surveys, 1960 to 1991. JAMA. 1994 Jul 20;272(3):205-11.

Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA. Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. Am J Epidemiol. 2002 Dec 1;156(11):1070-7.

Landrigan PJ, Schechter CB, Lipton JM, Fahs MC, Schwartz J. Environmental pollutants and disease in American children: estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. Environ Health Perspect. 2002 Jul;110(7):721-8

Lee PA, Guo SS, Kulin HE. Age of puberty: data from the United States of America. APMIS. 2001 Feb;109(2):81-8.

Leppig KA, Werler MM, Cann CI, Cook CA, Holmes LB. Predictive value of minor anomalies. I. Association with major malformations. J Pediatr 1987;110:530-7.

Lewit EM, Schuurmann Baker L, Corman H, Shiono P. (1995).The direct cost of low birth weight. Future Child.1995;5:35-56

Litonjua A.A. et al. A longitudinal analysis of wheezing in young children: The independent effects of early life exposure to house dust endotoxin, allergens and pets. Journal of Allergy and Clinical Immunology, 110:736-742 (2002).

Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. JAMA. 2002 May 8;287(18):2414-23

Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. Pediatrics. 1999 Mar;103(3):E26.

Lynberg MC, Edmonds LD. State use of birth defects surveillance. In: Wilcox LS, Marks JS editors. From Data to Action: CDC's Public Health Surveillance for Women, Infants, and Children Atlanta, GA: Centers for Disease Control and Prevention, US Department of Health and Human Services. 1994 pp. 217--26.

Maher Rasmussen K. The "fetal origins" hypothesis: challenges and opportunities for maternal and child nutrition. Annu Rev Nutr. 2001;21:73-95

Mallia P. et al. Respiratory viruses: Do they protect from or induce asthma? Allergy 57:1118-1129 (2002).

Mannino DM, et al. (2002). Surveillance for asthma – United States, 1980-1999. In: Surveillance Summaries, MMWR 2002;51(SS-1):1-13.

Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM. (2002)Births: Final data for 2000. National Vital Statistics Reports; vol 50, no 5. Hyattsville, MD: National Center for Health Statistics. 2002.

Martinez FD, Helms PJ. Types of asthma and wheezing. European Respiratory Journal 1998;27(suppl):3-8.

Martinez FD(2002). Development of wheezing disorders and asthma in preschool children. Pediatrics 2002;109:362-7.

Mattes J, Karmaus W. (1999). The use of antibiotics in the first year of life and development of asthma: which comes first? Clinical and Experimental Allergy 1999;29:729-32.

Mattson S.N. et al. Teratogenic effects of alcohol and brain and behavior. Alcohol Research and Health, 25:185-191 (2001).

McConnell R. et al. Indoor risk factors fro asthma in a prospective study of adolescents. Epidemiology, 13: 288-295 (2002).

Mendola P. et al. Environmental factors associated with a spectrum of neuropsychological deficits. Mental Retardation and Developmental Disabilities Research Reviews, 8:188-197 (2002).

MMWR. Economic costs of birth defects and cerebral palsy—United States, 1992; Sept 22, 1995;44(37);649-9.

Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991-1998. JAMA. 1999 Oct 27;282(16):1519-22.

Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, Rand WM. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? Am J Epidemiol. 2002 Apr 1;155(7):672-9.

Muto MA, Lobelle F Jr, Bidanset JH, Wurpel JN. Embryotoxicity and neurotoxicity in rats associated with prenatal exposure to DURSBAN. Vet Hum Toxicol. 1992 Dec;34(6):498-501

Naylor CD, Sermer M, Chen E, Sykora K. Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? Toronto Trihospital Gestational Diabetes Investigators. JAMA. 1996 Apr 17;275(15):1165-70

The National Children's Study Interagency Coordinating Committee. The National Children's Study of Environmental Effects on Child Health and Development. Environ Health Perspect (in press).

Needleman H.L. et al. Bone lead levels and delinquent behavior. Journal of the American Medical Association, 275:363-369 (1996).

Needleman H.L. et al. Bone lead levels in adjudicated delinquents. A case-control study. Neurotoxicology and Teratology, 24:711-717 (2002).

Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. I. Univariate analysis of risks. Am J Dis Child. 1985 Oct;139(10):1031-8.

Nelson KB, Willoughby RE. Overview: infection during pregnancy and neurologic outcome in the child. Ment Retard Dev Disabil Res Rev. 2002;8(1):1-2.

Nicklas TA, Baranowski T, Baranowski JC, Cullen K, Rittenberry L, Olvera N. Family and child-care provider influences on preschool children's fruit, juice, and vegetable consumption. Nutr Rev. 2001 Jul;59(7):224-35

Offenbacher S, Jarod HL, O'Reilly PG ,et al. (1998). Potential pathogenic mechanisms of periodontitis associated pregnancy complications. Ann Periodontal. 1998;3:233-50.

Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999-2000. JAMA. 2002 Oct 9;288(14):1728-32

Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ. 2000 Apr 8;320(7240):967-71.

Ott WJ. Sonographic diagnosis of intrauterine growth restriction. Clin Obstet Gynecol. 1997 Dec;40(4):787-95

Padungtod C, Niu T, Wang Z, Savitz DA, Christiani DC, Ryan LM, Xu X. Paraoxonase polymorphism and its effect on male reproductive outcomes among Chinese pesticide factory workers. Am J Ind Med. 1999 Sep;36(3):379-87.

Parnia S. et al. The role of pollutants in allergic sensitization and the development of asthma. Allergy, 57:1111-1117 (2002).

Parsons TJ, Power C, Logan S, Summerbell CD. Childhood predictors of adult obesity: a systematic review. Int J Obes Relat Metab Disord. 1999 Nov;23 Suppl 8:S1-107

Peden D. Pollutants and asthma: Role of air toxics. Environmental Health Perspectives, 110(suppl 4):553-556 (2002).

Ponsonby A.L. et al. Relationship between early life respiratory illness, family size over time, and the development of asthma and hay fever: a seven-year followup study. Thorax, 54:664-669 (1999).

Pottenger LH, Domoradzki JY, Markham DA, Hansen SC, Cagen SZ, Waechter JM Jr. The relative bioavailability and metabolism of bisphenol A in rats is dependent upon the route of administration. Toxicol Sci. 2000 Mar;54(1):3-18.

Redd S.C. Asthma in the United States: Burden and current theories. Environmental Health Perspectives, 110(suppl 4):553-556 (2002).

Rodier PM, Hyman SL. Early environmental factors in autism. MENT RETARD DEV D R 4 (2): 121-128 1998.

Romero R, Espinoza J, Chaiworapongsa T, Kalache K. (2002). Infection and prematurity and the role of preventive strategies. Semin Neonatol. 2002;7:259-74.

Romieu I, et al. (1998). Antioxidant supplementation and respiratory functions among workers exposed to high levels of ozone. American Journal of Respiratory and Critical Care Medicine 1998;158:226-32.

Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environ Health Perspect. 2001 Jul;109(7):675-80.

Salcido R, Costich JF. (1992). Recurrent traumatic brain injury. Brain Injury 1992;6:293-8.

Samet JM, et al. (2001). Effect of antioxidant supplementation on ozone-induced lung injury in human subjects. American Journal of Respiratory and Critical Care Medicine 2001;164:819-25.

Savitz DA, Ananth CV, Berkowitz GS, Lapinski R. Concordance among measures of pregnancy outcome based on fetal size and duration of gestation. Am J Epidemiol. 2000 Mar 15;151(6):627-33.

Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. Am J Obstet Gynecol. 1997 Nov;177(5):1165-71

Schonfelder G, Wittfoht W, Hopp H, Talsness CE, Paul M, Chahoud I. Parent bisphenol A accumulation in the human maternal-fetal-placental unit. Environ Health Perspect. 2002 Nov;110(11):A703-7.

Schunemann HJ, et al. (2002). Lung function in relation to intake of carotenoids and other antioxidant vitamins in a population-based study. American Journal of Epidemiology 2002;155:463-71.

Schwartz J, Weiss ST. (1990) Dietary factors and their relation to respiratory symptoms, The Second National Health and Nutrition Examination Survey. American Journal of Epidemiology 1990;132:67-76.

Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. Prev Med. 1993 Mar;22(2):167-77

Sinha R, Fisch G, Teague B, Tamborlane WV, Banyas B, Allen K, Savoye M, Rieger V, Taksali S, Barbetta G, Sherwin RS, Caprio S. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. N Engl J Med. 2002 Mar 14;346(11):802-10.

Story M, Neumark-Sztainer D, French S. Individual and environmental influences on adolescent eating behaviors. J Am Diet Assoc. 2002 Mar;102(3 Suppl):S40-51

Strachan DP. (2000). Family size, infection, and atopy: the first decade of the "hygiene hypothesis". Thorax 2000;55(S-1):2-10.

Taylor WR, Newacheck PW. (1992). Impact of childhood asthma on health. Pediatrics 1992;90:657-62.

U.S Department of Health and Human Services, Health Resources and Services Administration, Maternal and Child Health Bureau. *Child Health USA 2002.* Rockville, MD, 2002.

Viner R. Splitting hairs. Arch Dis Child. 2002 Jan;86(1):8-10.

von Hertzen, L.C. Maternal stress and T-cell differentiation of the developing immune system: Possible implications for the development of asthma and atopy. Journal of Allergy and Clinical Immunology, 109:923-928 (2002).

von Kries R, Koletzko B, Sauerwald T, von Mutius E, Barnert D, Grunert V, von Voss H. Breast feeding and obesity: cross sectional study. BMJ. 1999 Jul 17;319(7203):147-50

Warner CA, et al. (1998). Maternal programming in asthma and allergy). Clinical and Experimental Immunology 1998;28(suppl 5):35-8.

Weich S, Burton E, Blanchard M, Prince M, Sproston K, Erens B. Measuring the built environment: validity of a site survey instrument for use in urban settings. Health Place. 2001 Dec;7(4):283-92.

Weiss KB, Sullivan SD. (2001). The health economics of asthma and rhinitis. I. Assessing the economic impact. Journal of Allergy and Clinical Immunology 2001;107:3-8.

Whitaker RC, Dietz WH. Role of the prenatal environment in the development of obesity. J Pediatr. 1998 May;132(5):768-76

Wu T, Buck GM, Mendola P. Blood lead levels and sexual maturation in US girls: The Third National Health and Nutrition Examination Study, 1988-94. Environmental Health Perspectives. 2003, doi:10.1289/ehp6008.

Wu YW, Colford JM Jr. Chorioamnionitis as a risk factor for cerebral palsy: A meta-analysis. JAMA. 2000 Sep 20;284(11):1417-24

Xu F, Schillinger JA, Sternberg MR, Johnson RE, Lee FK, Nahmias AJ, Markowitz LE. Seroprevalence and coinfection with herpes simplex virus type 1 and type 2 in the United States, 1988-1994. J Infect Dis. 2002 Apr 15;185(8):1019-24.

Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. JAMA. 2003 Jan 1;289(1):49-55.

Yoon BH, Romero R, Park JS, Chang JW, Kim YA, Kim JC, Kim KS. Microbial invasion of the amniotic cavity with Ureaplasma urealyticum is associated with a robust host response in fetal, amniotic, and maternal compartments. Am J Obstet Gynecol. 1998 Nov;179(5):1254-60.